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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/602,521

06/24/2003

David Edwin Thurston

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EXAMINER

GROSS, CHRISTOPHER M

ART UNIT

PAPER NUMBER

1639

MAIL DATE

DELIVERY MODE

09/09/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/602,521	Applicant(s) THURSTON ET AL.	
	Examiner CHRISTOPHER M. GROSS	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 May 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 39-49 and 51-63 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 39-49, 54 and 58-60 is/are allowed.
- 6) ☒ Claim(s) 51-53, 55-57 and 61-63 is/are rejected.
- 7) ☒ Claim(s) 54-63 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>3/10/09; 6/4/09; 9/26/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Responsive to communications entered 5/11/2009. Claims 39-49,51-63 are pending. Claims 39-49,51-63 are examined herein.

Priority

This application was filed 6/24/2003 and is a CON of application 09/763,768 (referred to as '768) filed 02/26/2001 (now PAT 6,608,192) which is a 371 of PCT/GB99/02836 filed 08/27/1999.

Acknowledgment is further made of applicant's claim for foreign priority based on application no. 9818730.5 filed in the United Kingdom on 08/27/1998. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), in the parent case '768.

It is noted, however, an optional double bond between C1 and C2 such as set forth in present claims 51-53,55-57,61-63 is not disclosed in the UK application. Accordingly the earliest priority date for claims 51-53,55-57,61-63 is 8/27/1999.

The US filing date for claims 39-49,54, 58-60 is 08/27/1999 with foreign priority to UK application 9818730.5 filed 08/27/1998 is acknowledged.

Withdrawn Objection(s) and/or Rejection(s)

The rejection of claims 39-49,54,58-60 under 35 U.S.C. 103(a) as being unpatentable over **Baraldi et al** (1998 Bioorganic & Medicinal Chemistry Letters 8:3019-3024 – IDS entry 12/21/2007) in view of **Baird et al** (1996 JACS 118:6141-6146) is hereby withdrawn in view of applicant's amendments to the claims, antedating Baraldi et al by way of UK application 9818730.5 filed 08/27/1998.

The rejection of claims 39-49,54,58-60 under 35 U.S.C. 103(a) as being unpatentable over **Baraldi et al** (1998 Bioorganic & Medicinal Chemistry Letters 8:3019-3024 – IDS entry 12/21/2007) **in view of Baird et al** (1996 JACS 118:6141-6146) , and further in view of **Tam** (US Patent 5229490) is hereby withdrawn in view of applicant's amendments to the claims, antedating Baraldi et al by way of UK application 9818730.5 filed 08/27/1998.

The rejection of claims 54-63 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement concerning “new matter” is hereby withdrawn in view of applicant’s amendments to the claims.

The rejection of claims 54,58,59 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is hereby withdrawn in view of applicant’s amendments to the claims.

Maintained Claim Rejection(s) - 35 USC § 112

The following is a quotation of the **second** paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 51,52,53,55,56,57,61-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Each of claims 51,52,53,55,56,57,61-63 recite vague and indefinite language with regard to n and m. Each said claim states that n **is** a positive integer from 1 to 16

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and m is 1 except that one of n or m may be zero. It is not clear how m may be, for instance both 1 and 0 simultaneously or how n can be both positive and 0, therein rendering the metes and bounds of the offending claims unascertainable.

In accordance with MPEP 2173.02: If the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim so as to understand how to avoid infringement, a rejection of the claim under 35 U.S.C. 112, second paragraph, would be appropriate. See *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993).

Response to Arguments

On p 19 third paragraph of the remarks entered 5/11/ 2009, applicant argues, "Based on both the disclosure in the specification and the language in the claims, 'm' can be 0-1 and 'n' can be 0-16 with the proviso that **only** one of 'm' and 'n' may be 0." Emphasis added.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., **only** one of m and n may be zero) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Maintained Claim Rejection(s) - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 51,53 55,57, 61 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baraldi et al** (1998 Bioorganic & Medicinal Chemistry Letters 8:3019-3024 – IDS entry 12/21/2007) in view of **Baird et al** (1996 JACS 118:6141-6146).

Baraldi et al teach throughout the document and especially scheme 2, preparation of a pyrrolobenzodiazepine-distamycin conjugate, which reads on claims 51,53 55,57, 61 and 63 when: A=O; R₂=R₃=R₆=R₉=R₁₁=H; R₇ is methoxy; Y is an ethoxy chain; X' is CO and T and T'' are a N methylpyrrole amino acids; n is 1; m is 0; q is 0; R₁₀=Troc. Please note, N methylpyrrole amino acids, such as present in distamycin are included in the definition of amino acids set forth in paragraph 0089 of the present published application.

Baraldi et al do not teach: a collection of compounds, as set forth in the preamble to claims 51,53,55,57, 61 and 63; the solid support set forth in claims 54,55,57, 61 and 63.

Baird et al teach, throughout the document and especially figure 6, a manner of solid-phase synthesis directed to preparing various distamycin polyamide analogs. Said analogs are taken as a collection of compounds. Said solid phase synthesis of Baird et al includes a solid support (resin).

It would have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made to prepare various pyrrolobenzodiazepine-distamycin polyamide analogs per Baraldi et al with the solid-phase method according to Baird et al.

One of ordinary skill in the art would have been motivated to prepare various pyrrolobenzodiazepine-distamycin analogs per Baraldi et al with the solid-phase method according to Baird et al because it would circumvent challenges regarding variable coupling yields and numerous side products normally associated with preparing pyrrole polyamides in solution, as noted by Baird et al in the last paragraph on p 6141.

One of ordinary skill in the art would have had a reasonable expectation of success in preparing various pyrrolobenzodiazepine-distamycin analogs per Baraldi et al with the solid-phase method according to Baird et al because both references concern distamycin, thus the pyrrolobenzodiazepine-distamycin conjugate, prepared by Baraldi et al lies well within the scope of technology according to Baird et al.

Please note that the above rejection has been modified from the original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Response to Arguments

Applicant argues, see remarks entered 5/9/2009 not all elements are taught

Applicant's arguments have been fully considered but they are not deemed persuasive for the following reasons.

First, on p 20 penultimate paragraph applicant argues the compounds disclosed by Baraldi et al include a terminal amidine-containing aminoalkyl group that applicant asserts is not a feature presently claimed.

In this vein it is noted according to paragraph 0089 of the present specification, “The term ‘combinatorial unit’ means any monomer unit which can be used to build a chain attached to the solid support, **usually by a linking group... An important example of a unit is an amino acid residue.** Chains may be synthesised by means of **amine-protected amino acids.** Both natural and **unnatural amino acids can be used,**” Emphasis added. Here, in combining the teachings of the two references, one of skill in the art would necessarily replace the amidine-containing aminoalkyl group of Baraldi et al with Boc-beta alanine (an unnatural amine-protected amino acid derivative) as a linker to PAM resin, as advocated by Baird et al. Therein, as defined by applicant, said beta alanine reads on either an amino acid combinatorial unit, as set forth in claims 51,53 and/or the Linker ‘L’ set forth in claims 55,57, 61 and 63.

Second, in the paragraph bridging pp 20-21, applicant argues that neither reference suggests the solid-phase preparation of a collection of compounds. Applicant asserts that the teachings of Baird et al in figure 6 is limited to preparation of ImPyPy-gamma butyric acid-PyPyPy-betaDp.

In this vein, nowhere does Baird et al state that the method is limited to the preparation of ImPyPy-gamma butyric acid-PyPyPy-betaDp, and in accordance with MPEP 2144.01, “[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one

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skilled in the art would reasonably be expected to draw therefrom.” In re Preda, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). Here applicant’s attention is respectfully invited to p 6141, especially the paragraph bridging the left and right columns through the first full paragraph in the right column, where Baird et al that discuss preparation of various polyamide heterodimer and homodimers which bind to various double-stranded DNA sequences of interest. For example, a pyrrole/pyrrole pair targets DNA AT base pairs whereas a pyrrole/imidazole binds a DNA GC base pair. Along the same line, Baird et al state on p 6143 in the conclusion, “The large number of [different] polyamides made available by solid phase synthesis methodology should accelerate the elucidation of the scope and limitations of this approach.” Therefore in taking the reference as a whole, Baird et al at inherently discloses, or at least suggests, collections of various polyamides containing pyrrole amino acids, such as found in distamycin, that bind different DNA sequences.

Claims 52, 56 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baraldi et al** (1998 Bioorganic & Medicinal Chemistry Letters 8:3019-3024 – IDS entry 12/21/2007) **in view of Baird et al** (1996 JACS 118:6141-6146) as applied to claims 51, 53, 55, 57, 61 and 63 above, and further in view of **Tam** (US Patent 5229490)

Baraldi et al in view of Baird et al are relied on as above.

Baraldi et al in view of Baird et al do not teach the topological arrangement of amino acid combinatorial units, set forth in formulas XII, X, and XI of claims 52, 56 and

62 respectively, bearing, for instance two pyrrolobenzodiazepine groups: one on the main chain and a second on the side chain of an amino acid combinatorial unit.

Tam teaches, throughout the document and especially figure 1 and example 1, preparation of peptide dendrimers, by successive additions of Boc-Lys(Boc)-OH to a solid support. For example in example 1, after one round of coupling and deprotection of Boc-Lys(Boc)-OH, two free amines are generated: one main chain (alpha) and one side chain (epsilon) generating H-Lys-beta alanine -OCH₂PAM resin.

It would have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made to derivatize H-Lys-beta alanine -OCH₂PAM resin per Tam with compound 10 of Baraldi et al, for instance, so as to generate pyrrolobenzodiazepine-Lys(pyrrolobenzodiazepine)-beta alanine -OCH₂PAM type compounds, such as set forth in claims 52, 56 and 62.

One of ordinary skill in the art would have been motivated to prepare peptide dendrimers in the manner of Tam in concert with the pyrrolobenzodiazepine-distamycin analogs per Baraldi et al in view of Baird et al because, unlike other methods of preparing dendrimers, the exact structure is known, as noted by Tam in column 3 line 32, which would simplify discerning structure activity relationships.

One of ordinary skill in the art would have had a reasonable expectation of success in preparing peptide dendrimers in the manner of Tam in derivatized with the pyrrolobenzodiazepine-distamycin analogs per Baraldi et al in view of Baird et al because each reference concerns peptide synthesis, accordingly the synthetic strategy of Baraldi et al in view of Baird et al is completely compatible with that of Tam.

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Please note that the above rejection has been modified from the original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

In conclusion, the claimed invention was within the ordinary skill in the art to make and use at the time the claimed invention was made and was as a whole, *prima facie* obvious.

Response to Arguments

Applicant does not offer further arguments regarding the above obviousness rejections beyond what was set forth with regard to the 35 U.S.C. § 103 rejection, above. To the extent that Applicant is merely repeating their previous argument; the Examiner contends that those issues were adequately addressed in the above sections, which are incorporated in their entireties herein by reference.

New Claim Rejection(s) – 35 USC § 112

The following is a quotation of the **first** paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51,52,53,55,56,57,61-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

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reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection concerns “new matter.”

This rejection is necessitated by Applicant's amendment to the claims.

Each of claims 51,52,53,55,56,57,61-63 have been amended such that one of m or n may be zero, which includes the possibility that BOTH m and n may be zero. See also 35 USC 112 second paragraph rejection above.

While applicant asserts on p 19 third paragraph of the remarks entered 5/11/2009 that the amended language closely mirrors that found in the specification, applicant does not point to where said language may be found, especially with respect to the various formulas (VIII, etc.) recited in the rejected claims.

In this vein, applicants are reminded that it is their burden to show where the specification supports any amendments to the disclosure. See MPEP 714.02, paragraph 5, last sentence and also MPEP 2163.06 I.

MPEP 2163.06 notes “If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).” MPEP 2163.02 teaches that “Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should

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conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure.*

New Claim Objections

Claims 54-63 are objected to because of the following informalities: The symbol for the solid support should be a larger circle to avoid confusion with O, the chemical symbol for oxygen. Appropriate correction is required.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER M. GROSS whose telephone number is (571)272-4446. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571 272 0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christopher M Gross
Examiner
Art Unit 1639

cg

/ Christopher S. F. Low /
Supervisory Patent Examiner, Art Unit 16369